A Synopsis entitled

"Activity Guided Screening of Selected Botanicals for Management of Cancer"

Submitted to

Swami Ramanand Teerth Marathwada University,

Nanded-431606

For The Award Of Degree Of

Doctor Of Philosophy

In

Botany

Under the Faculty of

Science and Technology

By

Mr. Naiknaware Shyam Dnyanoba

M.Sc. SET,

Under the Guidance of

Dr. A. S. Kadam

M.Sc. Ph.D.

Professor and Head

Department of Botany

DSM's ACS College, Jintur

Dist. Parbhani-431509 (MS)

2022

"Activity guided screening of selected botanicals for management of Cancer"

Introduction:

Breast cancer continues to be the most frequently occurring cancer in women around the world. The increased incidence, mortality, economic costs, is a burden shared among women globally. Breast cancer continues to be a major public health problem in developed as well as developing countries. Unfortunately, in spite of improved diagnostic skills and breakthrough in effective treatment, Breast cancer continues to be the leading cause of cancer deaths among women worldwide, with approximately 375,000 deaths in the year 2000. Moreover, it is also accountable for greater than one million of the estimated 10 million diagnosed cancers worldwide each year in both sexes. One in ten of all new cancers diagnosed worldwide each year are a cancer of the female breast. The burden differs between countries and regions showing variations in incidence, mortality and survival rates. The age-standardized incidence of breast cancer is generally lower in developing countries than in developed countries (23.1 versus 63.2 per 100,000 women) however, the incidence rates vary widely between and within countries. Over the past several decades, the risk of breast cancer in developed countries has increased by one to two percent annually.

Breast cancer is cancer that develops from breast tissue. Signs of breast cancer may include a lump in the breast, a change in breast shape, dimpling of the skin, fluid coming from the nipple, or a red scaly patch of skin. In those with distant spread of the disease, there may be bone pain, swollen lymph nodes, shortness of breath, or yellow skin.

Risk factors for developing breast cancer include female sex, obesity, lack of physical exercise, drinking alcohol, hormone replacement therapy during menopause, ionizing radiation, early age at first menstruation, having children late or not at all, and older age. About 5–10% of cases are due to genes inherited from a person's parents, including BRCA1 and BRCA2 among others. Breast cancer most commonly develops in cells from the lining of milk ducts and the lobules that supply the ducts with milk. Cancers developing from the ducts are known as ductal carcinomas, while those developing from lobules are known as lobular carcinomas. In addition, there are more than 18 other sub-types of breast cancer. Some cancers develop from pre-invasive lesions such as ductal carcinoma in situ. The diagnosis of breast cancer is confirmed by taking a biopsy of the concerning lump. Once the diagnosis is made, further tests are done to determine if the cancer has spread beyond the breast and which treatments it may respond to.

Breast cancer is now the most commonly diagnosed cancer in urban Indian women. The reason for the recent observed increase in incidence of breast cancer in Indian population are not clearly understood but thought to be largely explained by 'Westernization' of lifestyles and changes in reproductive behaviour, compared to developed countries overall there were less cancer cases in India but that could be due to under diagnosis and under reporting. At the same time, regional, ethnic, dietary and socio-economic factors might also result in difference in the cancer susceptibilities and the incidence. In addition, cancer was mainly a disease of old ages. Worldwide median age at diagnosis was about 60 years. Average life span was about 58 yrs in India compared to 75 yrs in the developed world.

In recent years, oxidative stress and the mechanisms by which cancer is cause has been extensively studied. Cancer development is a multistage process which involves mutations in critical genes required for maintenance of the cellular homeostasis. Oxidative stress causes initiation, promotion and progression of carcinogenesis. ROS play an important role in the development of cancer. Oxidative damage to DNA or of antioxidant defence systems leads to mutation, activated transcription factors, modification of gene expression and chromosomal aberrations, processes that have been describe as the agents of progressions of cancer. There are many evidences that the generation of free radicals inside the body cause damages to DNA and lead to the development of cancer, etc., and if these free radicals are neutralized by the antioxidants from different medicinal plants, then it prevents cancer. Several studies have shown that plant derived antioxidant scavenge free radicals and modulate oxidative stress.

Review of literature and development in the subject (Previous work done in the relevant area):

Citrus fruits contain high concentration of several classes of phenols, including numerous hydroxycinnamates, flavonoids glycosides, and polymethoxylated flavones. The latter group of compound occurs without glycoside linkage and has been shown to inhibit the proliferation of a number of cancer cell lines. This antiproliferative property was further demonstrated against additional human cancer cell line and the antiproliferative action of series of synthetic methoxylated flavones were also studied. Similar to the naturally occurring compounds, the synthetic compounds exhibit strong antiproliferative activities. In many causes the IC_{50} values occurred below 10 *i*m. Other hydroxylated flavones and flavanone aglycons also exhibit antiproliferative activities against cancer cell line, with the flavones showing greater activities than flavanones. Glycosylation of these compound removed their

activity. The strong antiproliferative activities of the plymethoxylated flavones suggest that may have use as anticancer agents in humans (Johan and Najia, 2002).
The role of dietary flavonoids in cancer prevention is widely discussed. Compelling data from laboratory studies, epidemiological investigation, and human clinical trials indicates that flavonoids have important effect on cancer chemopreventation and chemotherapy. Many mechanism of action have been identified, including carcinogen inactivation, anti-proliferation, cell cycle arrest, induction of apoptosis and differentiation, inhibition of angiogenesis, antioxidant and reversal of multidrug resistance or a combination of these mechanism. Based on these result, flavonoids may be promising anticancer agent (Wenying et al., 2003)

Objective of research.

Considering the importance of the study the present investigation will be carried out with following objectives.

- Collection, identification and authentication of selected medicinal plant.
- Preparation of plant extracts by soxhlet method.
- Phytochemical screening of selected plant extracts
- Evaluate the anti-proliferative potential of selected medicinal plants against breast cancer cell line.
- Evaluate the anti-migratory potential of selected medicinal plants against breast cancer cell line.
- Evaluate the cytotoxicity of selected plant samples.
- Evaluate the anti-oxidant potential of selected medicinal plants.

Methods to be adopted.

- Collection of medicinal plant from local area.
- Preparation of plant extracts by soxhlet method using suitable solvent
- Qualitative and quantitative phytochemical analysis of selected medicinal plant.
- Evaluation of Migration capacity of the plant extract treated cells, by using scratch assay.
- Evaluation of the Cell Viability by using MTT assay of selected plant samples.
- Evaluation of cytotoxicity of selected plant.
- Evaluation of antioxidant potential of selected plant.

Importance of study/society application.

International status.

Breast cancer is the most common cancer diagnosed in women worldwide with over 1.3million new cases per year. There is a wide variation in the geographical burden of the disease with the highest incidences seen in the more developed regions of the world and the lowest incidences observed in the least developed regions. More recently, the incidence of breast cancer has been observed to be increasing in low-income countries and data suggest that over the next twenty years the majority of the increase in the worldwide burden of the disease will be due to rising incidences in these countries.

Breast cancer is the most prevalent cancer in the world (4.4 million survivors up to 5 years following diagnosis) and the second most common cause of cancer related mortality in women wide world. It also accounts for 23% (1.38 million) of the total new cancer cases and 14% (458,400) of the total cancer deaths in 2008 and ranks second most common cancer overall (10.9% of all cancers) but ranks fifth as cause of death. 1.15 million New breast cancer cases were recorded in 2004 and over 500,000 deaths reported around the world and more than half of all cases occurred in industrialized countries. Breast cancer incidence rates vary from 19.3 per 100,000 women in Eastern Africa to 89.7 per 100,000 women in Western Europe. They are normally high in developed regions of the world (except Japan) and low in most of the developing regions. Due to more favorable survival of breast cancer in developed regions, the range of mortality rates is very much less, approximately 6-19 per 100,000. Notwithstanding, it is still the most frequent cause of cancer death in women in both developing (269 000 deaths, 12.7% of total) and developed regions, where the estimated 189 000 deaths is almost equal to the estimated number of deaths from lung cancer (188 000 deaths).

National status.

Breast cancer is the commonest cancer in women worldwide with a widely variable incidence between countries and regions. The lowest breast cancer incidence is reported from Far Eastern and South-East Asian countries. In the developing countries of Asia, the health care burden on account of breast cancer has been steadily mounting. It is expected that in the coming decades, these countries would account for majority of new breast cancer patients diagnosed globally. Over 100,000 new breast cancer patients are estimated to be diagnosed annually in India. As per the ICMR-PBCR data, breast cancer is the commonest cancer among women in urban registries of Delhi, Mumbai, Ahmedabad, Calcutta, and Trivandrum where

it constitutes > 30% of all cancers in females (National Cancer Registry Program 1990-1996). In the rural PBCR of Barshi, breast cancer is the second commonest cancer in women after cancer of the uterine cervix (National Cancer Registry Program 1990-1996). The age standardized incidence rates (AARs) range from 6.2 to 39.5 per 100,000 Indian women. The AARs vary from region, ethnicity, religion, with the highest incidence reported at 48.3 per 100,000 women in the Parsi community of Mumbai (National Cancer Registry Program 1990-1996). The incidence of this disease has been consistently increasing, and it is estimated it has risen by 50% between 1965 and 1985. The rise in incidence of 0.5–2% per annum has been seen across all regions of India and in all age group but more so in the younger age groups (< 45 years). In general, breast cancer has been reported to occur a decade earlier in Indian patients compared to their western counterparts, while the majority of breast cancer patients in western countries are postmenopausal and in their 60ies and 70ies, the picture is quite different in India with premenopausal patients constituting about 50% of all patients. More than 80% of Indian patients are younger than 60 years of age. The average age of patients in 6 hospital-based cancer registries ranged from 44.2 years in Dibrugarh, 46.8 years in Delhi, 47 years in Jaipur, to 49.6 years in Bangalore and Chennai. A significant proportion of Indian breast cancer patients are younger than 35 years of age. This proportion varies between 11% (Tata Memorial Hospital (TMH) Mumbai) to 26% (SGPGIMS Lucknow). Young age has been associated with larger tumor size, higher number of metastatic lymph nodes, poorer tumor grade, low rates of hormone receptor-positive status, earlier and more frequent loco regional recurrences, and poorer overall survival.

Breast cancer is now the most commonly diagnosed cancer in urban Indian women. The reason for the recent observed increase in incidence of breast cancer in Indian population are not clearly understood but thought to be largely explained by ‘Westernization’ of lifestyles and changes in reproductive behavior, compared to developed countries overall there were less cancer cases in India but that could be due to under diagnosis and under reporting. At the same time, regional, ethnic, dietary and socio-economic factors might also results in difference in the cancer susceptibilities and the incidence. In addition, cancer was mainly a disease of old ages. Worldwide median age at diagnosis was about 60 years. Average life span was about 58 yrs in India compare to 75 yrs in the developed world.

Therefore, there is need to search for various plant origin constituents which will act as effective remedy against breast cancer. The present study may identify a novel compound from plant origin that might be use as a complementary therapy for the

successful management of breast cancer therapy. And the proposed work may be helpful for developing a novel and effective antioxidant and anti-breast cancer agent from plant origin.

Proposed work plan /formulation and structure of study.

Year wise plan of work and targets to be achieve.

Year I : literature search, course work and standardization of experimental protocols.

Year II : Collection and study of selected different plant samples on Breast cancer cell line, anti-oxidant studies, cytotoxicity studies

Year III : Research paper publication and thesis writing.

References:

1. Washbrook E. (2006). Risk fctors and epidemiology of breast cancer. Women's Health Med, 3, 8-14
2. Parkin DM, Bray F, Ferlay J, Pisani P. (2005): Global cancer statistics, 2002. CA Cancer J. Clin. 55, 74-108.
3. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. (2010): Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int. J. Cancer. 127, 2893–2917
4. Parkin DM and Fernandez LM.(2006): Use of statistics to assess the global burden of breast cancer. Breast J. 12, S70-S80.
5. Murthy NS, Agarwal UK, Chaudhry K, Saxena S: A study on time trends in incidence of breast cancer – Indian scenario. Eur J Cancer Care (2007); 16:185–6.
6. Freddie Bray, Peter McCarron and D Maxwell Parkin.(2004).The changing global patterns of female breast cancer incidence and mortality. Breast Cancer Res 2004, 6:229-239.
7. Dongwu Liu, Zhiwei Chen. 2013.The Effect of Curcumin on Breast Cancer Cells. J Breast Cancer (2013)June; 16(2): 133-137.
8. Ahmedin Jemal, DVM., Rebecca Siegel., Jiaquan Xu., Elizabeth Ward. Cancer Statistics, (2010). CA CANCER J CLIN 2010;60:277–300.

9. Dhanamani M., Lakshmi Devi S., and Kannan S. (2011). Ethnomedicinal plants for cancer therapy- a review. Hygeia. J D Med, 3(1), 1-10.
10. Dongwu Liu, Zhiwei Chen. (2013). The Effect of Curcumin on Breast Cancer Cells. J Breast Cancer 2013 June; 16(2): 133-137.

Mr.Shyam D.Naiknaware
(Researcher)

Prof A.S. Kadam
(Research supervisor)